SACHRP Recommendations on Single Patient Treatment Use

At the SACHRP meeting of October 4, 2011, FDA representatives asked SACHRP to provide feedback to FDA on several questions regarding treatment use of investigational drugs/biologics for individual patients, as allowed by 21 CFR 312.305 and 312.310. The representatives noted that FDA continues to hear from individual patients, caregivers, IRB members, and health care professionals that the administrative burdens associated with IRB review of expanded access are onerous and diminish its practicality, negatively impacting access to investigational drugs for treatment under expanded access protocols, particularly single patient treatment access protocols. The problem is particularly acute for physicians and patients that seek expanded access outside of institutional settings with an internal IRB.

The questions FDA asked included:

- What is the Committee's experience with IRB reviews of expanded access protocols?
- How quickly are they reviewed?
- Is there a charge to the individual?
- Are expanded access protocols able to be scheduled ahead of studies already on the calendar?
- Does providing for something like expedited IRB review seem a reasonable solution, based on the problem cited?
- If a reduction in the number of IRB members to approve an expanded access protocol is satisfactory to the Committee, does the Committee believe that mimicking the expedited review procedure is the best approach?
- What is the Committee's opinion on the risk/benefit analysis of expanded access protocols following the IRB procedure discussed in this presentation?

SACHRP agrees that substantial barriers exist to access to investigational drugs/biologics for treatment use, and that the problems are exacerbated for physicians and patients outside of an institutional setting. We offer the following comments and suggestions.

SACHRP notes that as a threshold issue, single patient access use does not involve the conduct of "research" as defined at 45 CFR 46 because there is no intent to develop generalizeable knowledge. Rather, this issue arises out of the FDA prohibition on the use of unapproved drugs, which requires that any use of an investigational drug must currently be considered within the regulatory framework for clinical investigations, primarily 21 CFR Parts 50, 56, and 312.

While the application of the FDA regulations regarding treatment use of investigational drugs/biologics for individual patients (21CFR 312.305 and 312.310) at the single site level with

a single patient does not represent research, it is important for IRBs, sponsors and FDA to recognize that the addition of more patients with similar indications begins to raise the need that research related to those indications should occur. Indeed, the Belmont Report is instructive on this point:

> "When a clinician departs in a significant way from standard or accepted practice, the innovation does not, in and of itself, constitute research. The fact that a procedure is 'experimental,' in the sense of new, untested or different, does not automatically place it in the category of research. Radically new procedures of this description should, however, be made the object of formal research at an early stage in order to determine whether they are safe and effective. Thus, it is the responsibility of medical practice committees, for example, to insist that a major innovation be incorporated into a formal research project.(3)" [Belmont Report]

In answer to the first four questions from FDA, the SACHRP and SOH members have had varying experience with IRB review of single patient expanded access protocols. However, despite our disparate experiences, common themes have emerged. First, reviews of treatment use are administratively burdensome because they involve unique documents and require coordination efforts that differ from the standard IRB review processes. As such, they involve extra time from IRB staff, chairs, and members. They are also difficult from an IRB perspective because they differ from the usual IRB function of reviewing research designed primarily to develop knowledge, as opposed to providing treatment to an identified individual patient. As to the time to review, some IRBs, depending on the setting, are able to review single patient expanded access protocols within a day or two. However, particularly in smaller institutional settings, it is often difficult to convene an ad hoc IRB meeting, as small institutions often have only one scheduled IRB meeting per month. In our collective experience, only independent IRBs charge for the review of single patient expanded access protocols, although some of the independent IRBs waive or reduce the standard IRB fee in these situations, either as standard procedure or upon request. In the experience of the membership of SACHRP and SOH, institution-based IRBs do not charge for these reviews, but we cannot confirm that this is universally true. Expanded access protocols can generally be scheduled ahead of other protocols, but more often the problem is one of arranging an ad hoc IRB meeting to review the expanded access protocol rather than moving that protocol ahead of other protocols in the queue for a scheduled IRB meeting.

SACRHP recommends the way to most immediately address this issue without any change to regulation or guidance is FDA issuance of more specific advice on how to obtain access to treatment use protocols. Currently the FDA website offers only limited advice, and to understand and utilize that advice the reader needs to have a solid understanding of the FDA regulations and their administrative support by FDA. The revised advice should provide a complete overview of the entire issue in one place, and should be understandable to physicians who do not normally conduct research and understandable to non-medically trained patients, as

patients and their relatives and loved ones often end up with the task of arranging the expanded access. The advice should include various scenarios. For instance, there are the necessary additional steps to take when the study article is not in the possession of the physician, and must be supplied by the sponsor in a time sensitive nature, and transportation of investigational product must be arranged. The advice should clearly address the role of each party in the process (FDA, sponsor/manufacturer, physician/investigator, IRB, and patient), and delineate in detail what steps must be taken sequentially, and which steps can be taken in any order as long as they are accomplished prior to use of the investigational product. It is often the case that one party or another (FDA, sponsor, investigator) believes that they cannot proceed until one of the other parties takes an action such as providing approval. It would also provide the most immediate assistance in easing the burden of the various parties involved in single patient expanded access protocols if FDA provided a template protocol, consent form, and any other documents necessary for single patient expanded access protocols. Much of the administrative burden associated with these protocols involves the development of such documents, often from scratch, and subsequent communications between the various involved parties to ensure that the documents are sufficient. This undertaking would provide the most immediate assistance in easing the burden of the various parties involved in single patient expanded access protocols, including patients. SACHRP notes that the American Society of Clinical Oncology (ASCO) issued a press release saying that it would provide guidance of this type, but it is not easy to find on the ASCO website[1], nor is it intuitive for all types of products that one should look to that website.

SACHRP believes that access to investigational drugs could be facilitated substantially if FDA continued to adhere to the "substance" of oversight requirements while being flexible as to "form." That is, certain substantive criteria must be met in order to allow expanded access, and these criteria should be assessed, with satisfaction of these elements documented. However, FDA could exercise enforcement discretion as to the form of review and allow individuals, or committees other than IRBs, to conduct this review, provided the review incorporates the required criteria.

This approach would offer greater flexibility to institutions, health care professionals and the patient community and would likely expedite access for patients, without compromising oversight standards. In addition, this more flexible approach may be better received by many IRBs, which are accustomed to reviewing traditional research protocols and sometimes do not feel comfortable or uniquely qualified to evaluate expanded access use. Given the strong federal policy reasons supporting expanded access, a degree of flexibility as to form of review is consistent with the policy and may even enhance it, as access would be facilitated in practice,

[1] See http://www.asco.org/ASCOv2/Press+Center/Latest+News+Releases/ASCO+News/ASCO+and+FDA+Work+Together+to+Help+Physicians+Secure+Investigational%2C+Unapproved+Drugs+For+Seriously+Ill+Patients+in+Need. SACHRP members were not able to find the resource on the ASCO website.

and substantive oversight would be maintained or even enhanced by the ability to tailor the review appropriately.

SACHRP believes the most efficient means to implement this flexible approach would be to issue guidance allowing the chair of the IRB, or another appropriate board member, to review the expanded access proposal and provide an appropriate opinion. CDRH has already issued guidance to this effect,[2] and if CDER and CBER followed this process as well much of the problem with IRB delay would be resolved.[3] It would need to be clear that this review is not expedited review, and it would be helpful to provide other administrative details, such as whether the single IRB member has the authority to disapprove the expanded use.

Alternatively, a possible approach is to allow IRBs to review treatment use protocols for individual patients through expedited review. SACHRP does not believe that allowing expedited approval of treatment use protocols for individual patients by IRBs is viable unless there is a change to the expedited review regulations at 21 CFR 56.110. In order to be eligible for expedited review, clinical investigations must be minimal risk and must be listed on the separate expedited categories list. These types of test article access rarely involve minimal risk. As the purpose of this access is treatment rather than research, SACHRP believes that a revision to the expedited regulations for this purpose would be a rational approach because, although there may be clinical risks from the treatment, there is no "research risk" involved in such single-patient treatment use.

SACHRP also recommends that there are several alternative approaches the agency might wish to consider. One is to invoke the IRB waiver that currently exists in the FDA regulations at 21CFR56.105. SACHRP recommends that FDA develop a form or format that a treating physician could file with FDA as a "sponsor-investigator" that would request a waiver of IRB review. FDA could develop a process of automatic approval or approval after a brief review of the form. It would be appropriate for the FDA to require the treating sponsor-investigator to notify the IRB with 5 days of such use and to require some form of patient consent as an additional safeguard.

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[2] Guidance on IDE Policies and Procedures, Chapter III, online at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf.

[3] SACHRP suggests that a change to existing FDA guidance would be useful in accomplishing this. Currently, the Information Sheet entitled "Emergency Use of an Investigational Drug or Biologic" states that "The FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore, "interim," "compassionate," "temporary" or other terms for an expedited approval process are not authorized. An IRB must either convene and give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval." On-line at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm. Many IRBs interpret this as not allowing a single board member to review single patient expanded access protocols.

Another approach would be to create ready access to a designated single patient access IRB. FDA's existing internal IRB could be that designated IRB. As an alternative to using FDA's internal IRB, FDA could provide a contract or special designation to an existing IRB, but regulatory authority and funding issues would need to be addressed.

Finally, SACHRP notes that FDA could modify 21 CFR 312 so that IRB review of single patient expanded access protocols is not required.

Finally, SACHRP recommends that FDA consider alteration of the current informed consent requirements for clinical investigations when applied to single patient expanded access protocols. Several of the elements of consent do not seem to apply to these protocols.

Regardless of the approach that FDA adopts, FDA and OHRP must work together to ensure that OHRP agrees to the approach.

SACHRP would be pleased to provide further information or opinion on any of the above issues if the input would be of value to the FDA. Patient access to investigational treatments is an critical issue, involving important and difficult principles such as protection of patients from unsafe and ineffective products, while at the same time allowing access for desperately ill patients who have exhausted other options.

Appendix of Relevant Regulations and Guidance

FDA Regulations

21 CFR 312, Subpart I - **Expanded Access to Investigational Drugs for Treatment Use**

Sec. 312.300 General.

(a) *Scope* . This subpart contains the requirements for the use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The aim of this subpart is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

(b) *Definitions* . The following definitions of terms apply to this subpart:

Immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

Sec. 312.305 Requirements for all expanded access uses.

The criteria, submission requirements, safeguards, and beginning treatment information set out in this section apply to all expanded access uses described in this subpart. Additional criteria, submission requirements, and safeguards that apply to specific types of expanded access are described in 312.310 through 312.320.

(a) *Criteria* . FDA must determine that:

(1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context

of the disease or condition to be treated; and

(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

(b)*Submission* . (1) An expanded access submission is required for each type of expanded access described in this subpart. The submission may be a new IND or a protocol amendment to an existing IND. Information required for a submission may be supplied by referring to pertinent information contained in an existing IND if the sponsor of the existing IND grants a right of reference to the IND.

(2) The expanded access submission must include:

(i) A cover sheet (Form FDA 1571) meeting the requirements of 312.23(a);

(ii) The rationale for the intended use of the drug, including a list of available therapeutic options that would ordinarily be tried before resorting to the investigational drug or an explanation of why the use of the investigational drug is preferable to the use of available therapeutic options;

(iii) The criteria for patient selection or, for an individual patient, a description of the patient's disease or condition, including recent medical history and previous treatments of the disease or condition;

(iv) The method of administration of the drug, dose, and duration of therapy;

(v) A description of the facility where the drug will be manufactured;

(vi) Chemistry, manufacturing, and controls information adequate to ensure the proper identification, quality, purity, and strength of the investigational drug;

(vii) Pharmacology and toxicology information adequate to conclude that the drug is reasonably safe at the dose and duration proposed for expanded access use (ordinarily, information that would be adequate to permit clinical testing of the drug in a population of the size expected to be treated); and

(viii) A description of clinical procedures, laboratory tests, or other monitoring necessary to evaluate the effects of the drug and minimize its risks.

(3) The expanded access submission and its mailing cover must be plainly marked "EXPANDED ACCESS SUBMISSION." If the expanded access submission is for a treatment IND or treatment protocol, the applicable box on Form FDA 1571 must be checked.

(c)*Safeguards* . The responsibilities of sponsors and investigators set forth

in subpart D of this part are applicable to expanded access use under this subpart as described in this paragraph.

(1) A licensed physician under whose immediate direction an investigational drug is administered or dispensed for an expanded access use under this subpart is considered an *investigator* , for purposes of this part, and must comply with the responsibilities for investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(2) An individual or entity that submits an expanded access IND or protocol under this subpart is considered a *sponsor* , for purposes of this part, and must comply with the responsibilities for sponsors set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(3) A licensed physician under whose immediate direction an investigational drug is administered or dispensed, and who submits an IND for expanded access use under this subpart is considered a *sponsor-investigator* , for purposes of this part, and must comply with the responsibilities for sponsors and investigators set forth in subpart D of this part to the extent they are applicable to the expanded access use.

(4)*Investigators* . In all cases of expanded access, investigators are responsible for reporting adverse drug events to the sponsor, ensuring that the informed consent requirements of part 50 of this chapter are met, ensuring that IRB review of the expanded access use is obtained in a manner consistent with the requirements of part 56 of this chapter, and maintaining accurate case histories and drug disposition records and retaining records in a manner consistent with the requirements of 312.62. Depending on the type of expanded access, other investigator responsibilities under subpart D may also apply.

(5)*Sponsors* . In all cases of expanded access, sponsors are responsible for submitting IND safety reports and annual reports (when the IND or protocol continues for 1 year or longer) to FDA as required by 312.32 and 312.33, ensuring that licensed physicians are qualified to administer the investigational drug for the expanded access use, providing licensed physicians with the information needed to minimize the risk and maximize the potential benefits of the investigational drug (the investigator's brochure must be provided if one exists for the drug), maintaining an effective IND for the expanded access use, and maintaining adequate drug disposition records and retaining records in a manner consistent with the requirements of 312.57. Depending on the type of expanded access, other sponsor responsibilities under subpart D may also apply.

(d)*Beginning treatment* --(1)*INDs* . An expanded access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA that the expanded access use may begin.

(2)*Protocols* . With the following exceptions, expanded access use under a protocol submitted under an existing IND may begin as described in 312.30(a).

(i) Expanded access use under the emergency procedures described in 312.310(d) may begin when the use is authorized by the FDA reviewing

official.

(ii) Expanded access use under 312.320 may begin 30 days after FDA receives the protocol or upon earlier notification by FDA that use may begin.

(3)*Clinical holds* . FDA may place any expanded access IND or protocol on clinical hold as described in 312.42.

Sec. 312.310 Individual patients, including for emergency use.

Under this section, FDA may permit an investigational drug to be used for the treatment of an individual patient by a licensed physician.

(a)*Criteria* . The criteria in 312.305(a) must be met; and the following determinations must be made:

(1) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition; and

(2) FDA must determine that the patient cannot obtain the drug under another IND or protocol.

(b)*Submission* . The expanded access submission must include information adequate to demonstrate that the criteria in 312.305(a) and paragraph (a) of this section have been met. The expanded access submission must meet the requirements of 312.305(b).

(1) If the drug is the subject of an existing IND, the expanded access submission may be made by the sponsor or by a licensed physician.

(2) A sponsor may satisfy the submission requirements by amending its existing IND to include a protocol for individual patient expanded access.

(3) A licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the expanded access request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient).

(c)*Safeguards* . (1) Treatment is generally limited to a single course of therapy for a specified duration unless FDA expressly authorizes multiple courses or chronic therapy.

(2) At the conclusion of treatment, the licensed physician or sponsor must provide FDA with a written summary of the results of the expanded access use, including adverse effects.

(3) FDA may require sponsors to monitor an individual patient expanded access use if the use is for an extended duration.

(4) When a significant number of similar individual patient expanded access

requests have been submitted, FDA may ask the sponsor to submit an IND or protocol for the use under 312.315 or 312.320.

(d)*Emergency procedures* . If there is an emergency that requires the patient to be treated before a written submission can be made, FDA may authorize the expanded access use to begin without a written submission. The FDA reviewing official may authorize the emergency use by telephone.

(1) Emergency expanded access use may be requested by telephone, facsimile, or other means of electronic communications. For investigational biological drug products regulated by the Center for Biologics Evaluation and Research, the request should be directed to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, 301-827-1800 or 1-800-835-4709, e-mail:*ocod@fda.hhs.gov* . For all other investigational drugs, the request for authorization should be directed to the Division of Drug Information, Center for Drug Evaluation and Research, 301-796-3400, e-mail:*druginfo@fda.hhs.gov* . After normal working hours (8 a.m. to 4:30 p.m.), the request should be directed to the FDA Emergency Call Center, 866-300-4374, e-mail:*emergency.operations@fda.hhs.gov* .

(2) The licensed physician or sponsor must explain how the expanded access use will meet the requirements of 312.305 and 312.310 and must agree to submit an expanded access submission within 15 working days of FDA's authorization of the use.

[74 FR 40942, Aug. 13, 2009, as amended at 75 FR 32659, June 9, 2010]

FDA Guidance on Treatment Use for Drugs and Biologics:

Emergency Use of an Investigational Drug or Biologic - Information Sheet

Guidance for Institutional Review Boards and Clinical Investigators

The emergency use of test articles frequently prompts questions from Institutional Review Boards (IRBs) and investigators. This information sheet addresses three areas of concern: emergency Investigational New Drug (IND) requirements; IRB procedures; and informed consent requirements.

Obtaining an Emergency IND

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test

article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means [21 CFR 312.310(d)].

FDA Contacts for Obtaining an Emergency IND

Product	Office/Division to Contact
drug products	Division of Drug Information[1] (888) 463-6332 (301) 796-3400
biological blood products	Office of Blood Research and Review (HFM-300) (301) 827-3518
biological vaccine products	Office of Vaccines Research (HFM-400) (301) 827-3070
On nights and weekends	Office of Crisis Management & Emergency Operations Center (866) 300-4374 (301) 796-8240

Emergency Exemption from Prospective IRB Approval

Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second

individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

Life-threatening, for the purposes of section 56.102(d), includes the scope of both life-threatening and severely debilitating, as defined below.

- **Life-threatening** means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.
- **Severely debilitating** means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis or stroke.

Institutional procedures may require that the IRB be notified prior to such use, however, this notification should not be construed as an IRB approval. Notification should be used by the IRB to initiate tracking to ensure that the investigator files a report within the five day time-frame required by 21 CFR 56.104(c). The FDA regulations do not provide for expedited IRB approval in emergency situations. Therefore, "interim," "compassionate," "temporary" or other terms for an expedited approval process are not authorized. An IRB must either convene and give "full board" approval of the emergency use or, if the conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without any IRB approval.

Some manufacturers will agree to allow the use of the test article, but their policy requires "an IRB approval letter" before the test article will be shipped. If it is not possible to convene a quorum of the IRB within the time available, some IRBs have sent to the sponsor a written statement that the IRB is aware of the proposed use and considers the use to meet the requirements of 21 CFR 56.104(c). Although, this is not an "IRB approval," the acknowledgment letter has been acceptable to manufacturers and has allowed the shipment to proceed.

This policy is undergoing review and is subject to change.

Exception from Informed Consent Requirement

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following [21 CFR 50.23(a)]:

1. The subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.

3. Time is not sufficient to obtain consent from the subject's legal representative.
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the test article is required to preserve the subject's life, and if time is not sufficient to obtain an independent physician's determination that the four conditions above apply, the clinical investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by a physician who is not participating in the clinical investigation. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23(c)].

Exception from Informed Consent for Planned Emergency Research

The conduct of planned research in life-threatening emergent situations where obtaining prospective informed consent has been waived, is provided by 21 CFR 50.24. The research plan must be approved in advance by FDA and the IRB, and publicly disclosed to the community in which the research will be conducted. Such studies are usually not eligible for the emergency approvals described above. The information sheet "Exception from Informed Consent for Studies Conducted in Emergency Settings: Regulatory Language and Excerpts from Preamble," is a compilation of the wording of 21 CFR 50.24 and pertinent portions of the preamble from the October 2, 1996 Federal Register.

http://www.fda.gov/RegulatoryInformation/Guidances/ucm126491.htm

FDA Guidance on Treatment Use for Devices:

Chapter III
Expanded Access to Unapproved Devices

According to the statute and FDA regulations, an unapproved medical device may normally only be used on human subjects when the device is under clinical investigation and when used by investigators participating in the clinical trial. FDA recognizes, however, that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient, to prevent irreversible morbidity, or to help a patient suffering from a serious disease or condition for which there exists no other alternative therapy. Below is a discussion of the four main mechanisms by which FDA may make unapproved devices available to patients/physicians faced with circumstances such as those described. These mechanisms are consistent with the Expanded Access provisions of the FDA Modernization Act of 1997 (See section 561 of the Federal Food, Drug, and Cosmetic Act). FDA plans to modify existing guidance in minor ways, as needed, to track the language in the new law.

Emergency Use of Unapproved Medical Devices
Procedures governing the emergency use of an investigational device are covered in two separate

documents: the IDE regulation (21 CFR Part 812) and FDA's "Guidance for the Emergency Use of Unapproved Medical Devices," (hereinafter referred to as the Emergency Use Guidance) which appeared in the **Federal Register** of October 22, 1985 (50 FR 42866).

The IDE regulation recognizes that emergency situations may arise in which there will be a need to use an investigational device in a manner inconsistent with the approved investigational plan or by a physician who is not part of the clinical study. Therefore, the regulation permits deviations from the investigational plan when necessary to protect the life or physical well-being of a subject in an emergency. (See 21 CFR 812.35(a)). Prior approval for shipment or emergency use of the investigational device is not required, but the use should be reported to FDA by the IDE sponsor via a supplement within 5 working days from the time the sponsor learns of the use. The supplement should contain a summary of the conditions constituting the emergency, the patient protection measures that were followed (as discussed below), and patient outcome information. In addition to the IDE regulation, emergency use is also addressed in an FDA guidance document.

The Agency issued the Emergency Use Guidance because the IDE regulation does not address emergency use comprehensively (e.g., by not defining the term "emergency use," identifying the patient protection measures that should be followed in such situations, or addressing emergency use of devices not covered by an IDE). This guidance defines an unapproved medical device as a device that is utilized for a purpose, condition, or use for which the device requires, but does not have, an approved application for premarket approval under section 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360e)(the act) or an approved IDE under section 520(g) of the act (21 U.S.C. 360j(g)). As discussed in the Guidance, an unapproved device should normally only be used in human subjects if it is approved for clinical testing under an IDE and if it is used by an investigator for the sponsor in accordance with the terms and conditions of the application. [18]Emergency use of an unapproved device, however, may also occur when: (i) an IDE for the device does not exist, (ii) when a physician wants to use the device in a way not approved under the IDE, or (iii) when a physician is not an investigator under the IDE.

The Emergency Use Guidance document was intended to address these *emergency* situations. As stipulated in the guidance, a physician who intends to treat a patient with an unapproved medical device in an emergency situation should conclude that:

1. The patient has a life-threatening condition that needs immediate treatment.†
2. No generally acceptable alternative treatment for the condition exists; and
3. Because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

FDA expects the physician to make the determination that the patient's circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. In the event that a device is used in circumstances meeting the criteria listed above, the physician should follow as many patient protection procedures as possible. Such patient protection procedures include obtaining:

1. Informed consent from the patient or a legal representative;

2. Clearance from the institution as specified by their policies;
3. Concurrence of the IRB chairperson;
4. An independent assessment from an uninvolved physician; and
5. Authorization from the IDE sponsor, if an approved IDE exists for the device.

Although not provided for under this guidance, often times a physician, who is faced with an emergency situation as described above, will contact FDA to discuss his/her patient's condition. In this situation, ODE acts in an advisory role, rather than in an approving role. The ODE employee who receives the call should discuss the emergency use criteria with the physician, but the responsibility for making the decision as to whether the situation meets the emergency use criteria and whether the unapproved device should be used lies with the physician. If the physician decides to proceed with the emergency use of the device, the ODE employee should advise the physician of the above patient protection procedures to be followed before the emergency use occurs and fill out the Emergency Use Checklist. This checklist helps to ensure that the criteria for emergency use have been met and that the physician has been informed that he/she is expected to follow as many patient protection procedures as possible. After discussing the situation with the physician and completing the checklist, it should be filed in the Emergency Use Report File located in the Program Operations Staff.

After the emergency use occurs, the treating physician is responsible for ensuring that certain follow-up procedures occur. If an IDE exists for the device, the physician should provide the IDE sponsor with sufficient patient follow-up information to allow the sponsor to comply with the reporting requirements of the IDE regulation. If no IDE exists, the physician should submit a follow-up report on the use of the device to the IDE Staff. This report should contain a summary of the conditions constituting the emergency, patient protection measures that were followed, and patient outcome information.

For more information on emergency use of investigational devices, see 50 FR 42866 and 21 CFR812.35(a).

Individual Patient Access to Investigational Devices Intended for Serious Diseases

As discussed above, the IDE regulation and the Emergency Use Guidance address those situations in which an investigational or unapproved device, respectively, is needed to save the life of a patient or to prevent irreversible morbidity. FDA recognizes, however, that there are circumstances in which an investigational device is the only option available for a patient faced with a serious, albeit not life-threatening condition (hereinafter referred to as "compassionate use"). In these circumstances, FDA uses its regulatory discretion in determining whether such use of an investigational device should occur. Unlike emergency use of an unapproved device, prior FDA approval is needed before compassionate use occurs. In order to obtain Agency approval, the sponsor should submit an IDE supplement requesting approval for a protocol deviation under section 812.35(a) in order to treat the patient. The IDE supplement should include:

† As a matter of practice, FDA has expanded the criteria of "life-threatening condition" to include serious diseases or conditions such as sight-threatening and limb-threatening conditions as well as other situations involving risk of irreversible morbidity. This is consistent with the new law.

1. A description of the patient's condition and the circumstances necessitating treatment;
2. A discussion of why alternatives therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition;
3. An identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient; and
4. The patient protection measures that will be followed. (These measures were previously discussed under the Emergency Use Guidance.)

The sponsor should not treat the patient identified in the supplement until FDA approves use of the device under the proposed circumstances. (IDE boilerplate G-16A has been developed for reviewers to use when addressing this type of request.) In reviewing this type of request, FDA will consider the above information as well as whether the preliminary evidence of safety and effectiveness justifies such use and whether such use would interfere with the conduct of a clinical trial to support marketing approval.

If the request is approved, the attending physician should devise an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient. The patient should be monitored to detect any possible problems arising from the use of the device. Following the compassionate use of the device, a follow-up report should be submitted to FDA as an IDE supplement in which summary information regarding patient outcome is presented. If any problems occurred as a result of device use, these should be discussed in the supplement and reported to the reviewing IRB as soon as possible.

The above compassionate use criteria and procedures can also be applied when a physician wishes to treat a few patients rather than an individual patient suffering from serious disease or condition for which no alternative therapy adequately meets the medical need. In this case, the physician should request access to the investigational device through the IDE sponsor. The sponsor should submit an IDE supplement that includes the information identified above and indicates the number of patients to be treated. Such a supplement should include the protocol to be followed or identify deviations from the approved clinical protocol. As with single patient compassionate use, a monitoring schedule should be designed to meet the needs of the patients while recognizing the investigational nature of the device. Follow-up information on the use of the device should be submitted in an IDE supplement after all compassionate use patients have been treated.

Treatment Use of Investigational Devices
Provisions of the Regulation

In the **Federal Register** of September 18, 1997 (62 FR 48940), FDA established procedures to allow for the treatment use of investigational devices. These procedures are intended to facilitate the availability of promising new therapeutic and diagnostic devices to desperately ill patients as early in the device development process as possible, i.e., before general marketing begins, and to obtain additional data on the device's safety and effectiveness. These procedures apply to patients with serious or immediately life-threatening diseases or conditions for which no comparable or satisfactory alternative device, drug, or other therapy exists.

Under the final rule, treatment use of an investigational device will be considered when:

1. The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition;
2. There is no comparable or satisfactory alternative device available to treat or diagnose the disease or condition in the intended patient population;
3. The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or all clinical trials have been completed; and
4. The sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational device with due diligence.

Procedures
If a sponsor is considering submitting a treatment IDE, the sponsor should consult with the appropriate review division in order to determine if the device/indication would meet the criteria for approval. Note that treatment IDEs are limited to those devices/indications which meet the criteria defined above. According to 21 CFR 812.36, requests for treatment use should be submitted as a supplement to the existing IDE and should include:

1. The name, address, and telephone number of the sponsor of the treatment IDE;
2. The intended use of the device, the criteria for patient selection, and a written protocol describing the treatment use;
3. An explanation of the rationale for the use of the device, including either a list of the available regimens that ordinarily should be tried before using the device or an explanation of why the use of the device is preferable to the use of available marketed treatments;
4. A description of clinical procedures, laboratory tests, or other measures to be used to monitor the effects of the device and to minimize risk;
5. Written procedures for monitoring the treatment use and the name/address of the monitor;
6. Instructions for use and all labeling for the device as required under section 812.5(a) and (b);
7. Information relevant to the safety and effectiveness of the device for the intended treatment use;
8. A statement of the sponsor's commitment to meet all applicable responsibilities under Parts 812 and 56 and to ensure compliance of all participating investigators with Part 50;
9. An example of the investigator agreement to be signed by all investigators and certification that no investigator will be added to the treatment IDE before the agreement is signed; and
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10. If the device is to be sold, the price to be charged and a statement that the price is based on manufacturing and handling costs only.

As with all IDEs, treatment IDEs may begin 30 days after FDA receives the application, unless FDA notifies the sponsor earlier than 30 days that the treatment use may or may not begin. The Agency may approve the treatment use as proposed, approve it with modifications/conditions, or disapprove it. FDA may withdraw approval of the treatment IDE if it is determined that the above criteria are no longer met.

In order to protect the rights, safety, and welfare of human subjects involved in the clinical trial,

while at the same time facilitating the development of beneficial device therapies, FDA included certain safeguards in the Treatment IDE process. Some of these measures were already in place as part of the IDE regulation, while other safeguards were specifically designed for treatment use.

Safeguards for this process include: the distribution of the device through qualified experts; maintenance of adequate manufacturing facilities; the submission of reports pursuant to 21 CFR 812.150; and compliance with the regulations governing informed consent and institutional review boards. Sponsors should review these sections of the regulation when preparing a Treatment IDE application to ensure that these issues are properly addressed.

When an IDE supplement requesting approval for treatment use is received in the reviewing division, the reviewer should immediately notify the IDE Staff. The IDE Staff will assist the division with the review of the application to ensure that all applicable safeguards have been satisfied and that all of the criteria identified in the regulation (see above) have been adequately addressed before the application can be approved. Three boilerplate letters are available for responding to requests for treatment use: G-46 for approval, G-47 for conditional approval, and G-48 for disapproval.

ODE review divisions should note that the IDE tracking sheets include a reason-for-submission code for Treatment IDE supplements. It is important that the division indicate on the tracking sheets that the application was a Treatment IDE, so that these applications can be properly tracked.

The Treatment IDE regulation is effective on January 16, 1998. For further guidance on Treatment IDEs, see the **Federal Register** of September 18, 1997 (62 FR 48940) or contact the IDE Staff at (301) 594-1190.

http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf.